Claims 1-84 are pending in the instant application. Claims 1, 81 and 82 have been amended. No new matter has been added.

I.   Claim Objections

Claim 81 stands objected to for alleged improper multiple dependency.

Applicants have amended Claim 81 to overcome this objection.

II.   Claim Rejections under 35 U.S.C. §112, Second Paragraph

Claims 1-80 and 82-84 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Particularly:

Claims 1 and 82 stand rejected for allegedly being indefinite for reciting the limitation "the sequence in the sequence database" with insufficient antecedent basis. In accordance with the Examiner's suggestion, said claims are currently amended to overcome the rejection by reciting "a sequence in the sequence database."

Claims 1 and 82 further stand rejected for allegedly being indefinite for reciting the limitation "the de novo sequence" with insufficient antecedent basis. In accordance with the Examiner's suggestion, said claims are currently amended to overcome the rejection by reciting "the at least one de novo sequence."

These amendments are believed to be sufficient to overcome the instant rejections to Claims 1 and 82, as well as those claims dependent thereupon.

III.   The Rejections under 35 U.S.C. § 101

Claims 1-80 and 82-84 stand rejected for allegedly directing to non-statutory subject matter.

Applicants respectfully disagree and submit that the limitation in Claim 1 that reads "storing said macromolecule list on a computer readable medium" and in Claim 82 that reads "storing said score on a computer readable medium" produces tangible results and are therefore believed to be directed to statutory subject matter.

According to MPEP 2106.01, when functional descriptive material is recorded on some computer-readable medium, it becomes structurally and functionally interrelated to the medium and will be statutory in most cases since use of technology permits the function of the descriptive material to be realized. *In re Lowry*, 32 F.3d 1579, 1583-84, 32 USPQ2d 1031, 1035.

The Examiner asserts that "[t]he recited database is further not limited to only physical computer readable media, but further transient embodiments such as a carrier wave and signal." (Page 9 of the instant Final Office Action).

Applicants submit that descriptive material can be characterized as either "functional descriptive material" or "nonfunctional descriptive material." In this context, as in the instant claims, "functional descriptive material" consists of data structures and computer programs which impart functionality when employed as a computer component. MPEP 2106.01. Further, a claimed computer-readable medium encoded with a data structure defines structural and functional interrelationships between the data structure and the computer software and hardware components which permit the data structure's functionality to be realized, and is thus statutory. MPEP 2106.01 (I)

Support for the functionality of the computer-readable medium employed in the instantly claimed methods can be found throughout the original specification and specifically at least in Figures 4 and 5, as well as paragraphs 0043 and 0080. Accordingly, since Claims 1-80 and 82-84 are believed to be directed to statutory subject matter, Applicants respectfully request withdrawal of present rejection.

IV.   The Rejections under 35 U.S.C. §103(a)

Claims 1-12, 63-80 and 82-84 stand rejected under §103(a) as being unpatentable over Dancik *et al.* (Journal of Computational Biology, 1999, volume 6, pp. 327-342) in view of Pevzner *et al.* (Genome Research, 2001, volume 11, pp. 290-299).

Applicants respectfully disagree and traverse the rejection.

Assuming that it would be proper to combine the references, Applicants assert that such a combination would not reach the present invention.

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Applicants respectfully submit the following factual summary on why the present invention is not obvious in view of the cited art. (1) Dancik *et al.* in view of Pevzner *et al.* do not teach interpreting mass differences between the sequence in the sequence database and the *de novo* sequence using a modification catalog, said mass differences having been identified within said mass-based alignment. (2) Dancik *et al.* in view of Pevzner *et al.* do not teach grouping identifications of sequences in the sequence database from at least one *de novo* sequence into an identified macromolecule list that agrees with the *de novo* sequencing results. (3) The present invention claims a method that is capable of characterizing a greater number of specific isobaric equivalences, making it possible to separate de novo sequencing errors from actual sequence modifications, analyzing sequences from poor quality spectra and identifying post-translational modifications all in a high throughput environment, thus meeting a long felt need for the identification of proteins that match de novo sequences to homologous proteins. (4) As discussed in greater detail below, Pevzner *et al.* specifically teach away from the present invention on a number of these features.

The Examiner asserts that "[n]either the instant claims nor the instant specification provide a limiting definition for the contents of 'a modification catalogue' that would exclude the listings of a plurality modified peptides as taught by Pevzner et al." (Page 18 of the instant Final Office Action).

Applicants respectfully disagree and point out that the instant specification discloses adequate description of a modification catalog as used in the instant invention. For example, paragraphs 0029-0032 and 0043-0045 of the instant specification disclose that "mass differences of modification sites between the sequence in the sequence database and the de novo sequence that have been identified by the mass-based alignment are interpreted as modifications identified in a modification catalog." Further, Claim 42 discloses, "wherein said modification information includes at least one of, molecular mass of the modification, specific fragments where the modification occurs, a frequency of occurrence of the modification at those fragments, wherein the frequency of occurrence is the estimated frequency in nature or a frequency as a sample preparation artifact, a mass object for the modification, which represents

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the additional mass of the modification to the *de novo* sequence at those fragments, the name of the modification, and a modification score for the modification." Claim 43 further discloses, "wherein a modification is selected from, an in vivo or in vitro protein, a peptide modification, and an amino acid substitution." Paragraph 0046 goes on to state "In one embodiment of the present invention, mass-based alignment of de novo sequences are utilized to accurately identify sequence variations and post-translational protein modifications, thus allowing for these types of searches to succeed in a high-throughput environment."

Applicants submit that Pevzner does not teach a modification catalog of any kind, let alone for interpreting <u>mass differences</u> between a de novo sequence and a sequence in a sequence database identified by mass-match alignment. The listings of peptides in Figures 1 and Table 1 of Pevzner are merely examples to illustrate the application of their method. Figure 1 of Pevzner is a <u>theoretical spectra</u> of peptides intended to demonstrate their "Shared Peaks Count" method. In fact, in the disclosure of this method, Pevzner teach away from identifying and/or cataloging the molecular mass of a modification as in the instant application. As stated in the 2nd paragraph of column 2 on page 292, Pevzner *et al* teach, "For the sake of simplicity, we represent a spectrum S as a set of integers, corresponding to masses of fragment ions and <u>ignore the intensities</u> of the fragment ions." Furthermore, at the end of the same paragraph, Pevzner teaches "SPC [Shared Peaks Count] is, of course, an <u>intuitive measure</u> of spectral similarity. However, <u>this measure diminishes very quickly as the number of mutations increases</u> thus leading to limitations in detecting similarities in MS/MS database search." The peptides listed in Table 1 of Pevzner *et al* are merely an accounting of the sample peptides matched against the yeast protein database using their disclosed algorithms. This table does not provide information for interpreting mass differences between a de novo sequence and a sequence in a sequence database identified by mass-match alignment.

The Examiner further asserts that "the features upon which applicant relies (i.e. interpreting mass differences and identifying the specific medications [modifications]) are not recited in the rejected claims." Specifically, the Examiner asserts that "the

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claims do not recite any limitation that requires a specific modification be identified."
(Page 19 of the instant Final Office Action).

Applicants disagree and submit that the instant claims recite "interpreting mass
differences between a sequence in the sequence database and the at least one *de
novo* sequence using a modification catalog, said mass differences having been
identified within said mass-based alignment." As stated above, the instant application
discloses that "modification information includes at least one of, molecular mass of the
modification, specific fragments where the modification occurs, a frequency of
occurrence of the modification at those fragments, wherein the frequency of occurrence
is the estimated frequency in nature or a frequency as a sample preparation artifact, a
mass object for the modification, which represents the additional mass of the
modification to the *de novo* sequence at those fragments, the name of the modification,
and a modification score for the modification."

Pevzner *et al.* do not teach the identification and characterization of any
modifications, using a modification catalog or otherwise, but instead teach a
mutation/modification –"tolerant" method that "reliably identifies peptides differing by up
to two mutations/modifications from a peptide database." (Page 290, Abstract). That is,
they are able to identify peptide matches in a database in spite of the presence of a
mutation/modification in a peptide. However, Applicants would like to further point out
that the Pevzner technique involves matching ion series in MS/MS spectra to peptide
sequences without using a stringent parent ion mass filter. This approach comes with a
tradeoff in the accuracy of its scoring function that often assigns high scores to incorrect
peptide identification by chance (page 298, column 1, paragraph 2), thereby limiting its
application in high-throughput environments, such as described in the instant
specification.

Further, Applicants submit that Pevzner teaches away from the many of the
novel features of the present invention claims, such as the capability to 1) characterize
a multitude of specific isobaric equivalences and thus make it possible to separate de
novo sequencing errors from actual sequence modifications, 2) analyzing sequences
from poor quality spectra and 3) identifying post-translational modifications in a high

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throughput environment. For example, as stated above, Pevzner teach a mutation/modification –"tolerant" method that "reliably identifies peptides differing by up to two mutations/modifications from a peptide database." (Page 290, Abstract). As disclosed in the instant specification, the sequence homology approach used by the prior art can only consider a small number of specific isobaric equivalences. By contrast, Example 5 of the instant specification demonstrates that the methods and systems of the present invention were able to identify 12 sites of single amino acid variance in amniotic fluid lactotransferrin.

As demonstrated in Example 3 of the instant specification, the methods and systems of the present invention allows low abundance proteins with poor coverage to be found, even if proteins with higher coverage dwarf them. Further, this approach can find short, isobaric equivalences of an arbitrary residue length, in this case, three consecutive residues or masses, within a given mass tolerance (paragraph 0056 of the instant specification). However, Pevzner acknowledge that while their method places correct peptides among the 500 top-scoring peptides in most cases, spectra of very short peptides and low quality spectra are an exception. (page 299, 1st paragraph of column 1).

Finally, as demonstrated in Example 6 of the instant specification, the methods and systems of the present invention allowed the identification of six different types of modifications in a human lens crystalline sample. By contrast, Pevzner teaches that "a number of questions related to modification-tolerant MS/MS database searches remain open." (page 299, 3rd paragraph, column 1). Moreover, Pevzner discloses that their method does not rely on a prior knowledge of possible types of modifications. (page 294, 3rd paragraph of column 2).

Accordingly, the instant claims are not obvious over Dancik et al. in view of Pevzner et al. and Pevzner et al repeatedly teach away from the present invention. Thus, Applicants respectfully request withdrawal of the present rejection.

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The Examiner has rejected Claims 1-27, 63-80 and 82-84 under §103(a) as allegedly being unpatentable over Dancik *et al.* in view of Pevzner *et al.* and further in view of Mann *et al.* (Analytical Chemistry, 1994, volume 66, pp. 4390-4399).

As discussed above, and in the previously filed Response of July 2, 2007, Dancik *et al.* in view of Pevzner *et al.* do not disclose each and every limitation of Claims 1 or 82, nor those claims dependent thereupon, for at least the reasons given above. Mann *et al.* do not cure the deficiencies of Dancik *et al.* in view of Pevzner *et al.*, as Mann *et al.* do not teach methods for: 1) interpreting mass differences between the sequence in the sequence database and the *de novo* sequence using <u>a modification catalog</u>, said mass differences having been identified within said mass-based alignment, or 2) grouping identifications of sequences in the sequence database from at least one *de novo* sequence into an <u>identified macromolecule list</u> that agrees with the *de novo* sequencing results.

The Examiner has rejected Claims 1-80 and 82-84 under §103(a) as being unpatentable over Dancik *et al.* in view of Pevzner *et al.* in view of Mann *et al.* and further in view of Bader (Bioinformatics, 2003, volume 19, pp. 1869-1874).

As discussed above, and in the previously filed Response of July 2, 2007, Dancik *et al.* in view of Pevzner *et al.* and further in view of Mann *et al.* do not disclose each and every limitation of Claim 1 and 82 or those claims dependent thereupon. Bader *et al.* do not cure the deficiencies of Dancik *et al.*, Pevzner *et al.* and Mann *et al*, as Bader *et al.* do not teach a method for identifying a macromolecule having a sequence and sequence modifications thereof from mass spectrometry data following the steps recited in the claims of the instant application.

Accordingly, the instant claims are not obvious over the above-cited references Thus, Applicants respectfully request withdrawal of the present rejection.

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CONCLUSION

Applicant respectfully requests that a timely Notice of Allowance be issued in this case. If any points remain that can be resolved by telephone, the Examiner is invited to contact the undersigned at the below-given telephone number.

Please charge any fees, including fees for extension of time, or credit overpayment to Deposit Account No. **07-1700**, referencing Attorney's Docket No. **PTX-0003**.

Respectfully submitted,

Date: June 3, 2008

By: _____

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